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Functional Assessment of Jailed Side Branches in Coronary Bifurcation Lesions Using Fractional Flow Reserve

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Objectives This study was designed to assess the functional significance of side branches after stent implantation in main vessels using fractional flow reserve (FFR).

Background Little is known about the functional significance of side branches after stent implantation in main vessels in coronary bifurcation lesions.

Methods Between May 2007 and January 2011, 230 side branches in 230 patients after stent implantation in main vessels were assessed by FFR and were consecutively enrolled.

Results Median FFR at the side branch was 0.91 (interquartile range: 0.85 to 0.95). There was a negative correlation between the diameter stenosis (DS) by quantitative coronary angiography (QCA) and FFR of side branch ($r = -0.21$, $p = 0.002$), but only 41 (17.8%) side branches were functionally significant after stent implantation in the main vessel. Among 67 side branches with >50% DS by QCA, 19 (28.4%) had FFR ≤0.80, and among 163 side branches with ≤50% DS by QCA, 22 (13.5%) had FFR ≤0.80 after stent implantation in main vessels. On the basis of receiver-operating characteristic curves, the optimal cutoff value of DS by QCA of the side branch was 54.9%, and the area under the curve was 0.64 (95% confidence interval [CI]: 0.58 to 0.71, $p < 0.001$) with a 41.5% sensitivity, an 83.1% specificity, a 34.7% positive predictive value, an 86.3% negative predictive value, and a 75.7% accuracy. Multivariate binary logistic regression analysis identified DS by QCA (odds ratio [OR]: 1.04, 95% CI: 1.02 to 1.06, $p = 0.001$) and reference vessel diameter (OR: 0.28, 95% CI: 0.10 to 0.77, $p = 0.014$) before stent implantation as independent predictors of the side branches with FFR ≤0.80 after stent implantation.

Conclusions Most side branch lesions do not have functional significance after stent implantation in the main vessel, and quantitative coronary angiography is unreliable in assessing the functional severity of these lesions. (J Am Coll Cardiol Intv 2012;5:155–61) © 2012 by the American College of Cardiology Foundation

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Percutaneous coronary intervention for coronary bifurcation lesions remains technically challenging. Although angiographic stenosis of a side branch ostium is frequently observed after stent implantation in a main vessel, the clinical advantages of treating these lesions using complex interventional strategies remain unclear (1–3), and such interventions may increase the subsequent risk of adverse clinical events (4,5). In addition, these lesions cannot be properly evaluated by conventional coronary angiograms (6,7).

Fractional flow reserve (FFR) is a pressure-derived, lesion-specific index used to determine the functional significance of coronary artery stenosis (8). FFR has been shown to be safe and feasible in assessing jailed side branches. FFR also demonstrated the discrepancy between the angiographic and functional significance of jailed side branches, with only a minority of the angiographically jailed side branches having functional significance (9,10). These findings have profound implications in guiding strategies of bifurcation coronary artery stenosis management. However, these studies examined a limited number of lesions and did not use dedicated bifurcation quantitative coronary angiography (QCA) analysis (6). To determine the incidence and predictors of functionally significant side branch stenosis and to compare the FFR value with QCA parameters, we measured FFR of side branches after stent implantation in main vessels in a large number of coronary bifurcation lesions.

Abbreviations and Acronyms

AUC = area under the curve

CI = confidence interval

DS = diameter stenosis

FFR = fractional flow reserve

IQR = interquartile range

MLD = minimal lumen diameter

OR = odds ratio

QCA = quantitative coronary angiography

Methods

Study population. Between May 2007 and January 2011, 241 consecutive patients with a total of 241 side branches with coronary bifurcation lesions and meeting the inclusion and exclusion criteria of the current study were selectively enrolled, but 11 lesions in 11 patients were not assessed by FFR after stent implantation in the main vessel due to guidewire passing failure (n = 7) and side branch dissection (n = 4). Finally, 230 patients with a total of 230 lesions were enrolled in the current analysis. Inclusion criteria were a side branch with a minimum diameter >2 mm, <10 mm in lesion length of the side branch ostium by visual estimation, and Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the side branch flow after stent implantation in the main vessel. Patients with regional wall motion abnormalities in the main vessel or side branch territories, ejection fraction <40%, bypass graft lesions, a significant distal lesion within the side branches, a significant lesion within the main vessel proximal to the stented segment, in-stent restenosis, thrombus-containing lesions, predilation of side branches before FFR measurement, and contraindication to adenosine were excluded. Our institutional review board approved the use of clinical data for this study, and all patients provided written informed consent.

Angiographic analysis and definition. Angiograms were independently analyzed using a dedicated bifurcation angiographic software (CAAS version 5.4, Pie Medical Imaging, Maastricht, the Netherlands) in the angiographic core laboratory of the CardioVascular Research Foundation (Seoul, Korea) (7). QCA of each bifurcation lesion was obtained in 3 segments: the proximal and distal main vessel segments and the side branch. Bifurcation types were categorized according to the classification of Medina (11). For quantitative analysis, at least 2 orthogonal projections were obtained, and the angiographic frames with homogeneous contrast filling of the segment of interest were selected in a view offering good opening of the bifurcation, no overlap from other vessels and side branches, and absence of major vessel foreshortening. Quantitative angiographic parameters in the proximal and distal main vessels and the side branches were measured at baseline and after stent implantation in the main vessel. According to the algorithm in the dedicated software, lesion length, reference diameter, minimal lumen diameter (MLD), diameter stenosis (DS), and bifurcation angle were measured (7). Main vessel lesions were classified as types A and B when the MLD site was located in the main vessel proximal and distal, respectively, to the takeoff of the side branch (12). Angiographically significant side branch stenosis was defined as >50% DS within the side branch ostium.

Procedure and FFR measurement. Coronary stenting of the main vessel with or without adjunctive balloon dilation was performed using standard interventional techniques and drug-eluting stents (Cypher, n = 84 [Cordis, Bridgewater, New Jersey]; Xience V, n = 56 [Abbott Vascular, Santa Clara, California]; Endeavor, n = 60 [Medtronic, Minneapolis, Minnesota]; Taxus, n = 21 [Boston Scientific, Natick, Massachusetts]; others, n = 9), with a single-stent crossover stenting strategy (13). After the measurement of FFR, the decision to treat the side branch lesions was at the discretion of the operator.

After successful stent implantation in the main vessel, FFR measurements were performed using 0.014-inch pressure guidewires (St. Jude Medical, Minneapolis, Minnesota) as described previously (9). Briefly, the pressure guidewire was passed through the struts of the stent in the main vessel, and FFR was measured at least 5 mm distal to the side branch ostium. Maximal hyperemia was induced by intravenous infusion of 140 μg/kg/min adenosine through a central or antecubital vein. Hyperemic pressure pull-back recordings were performed to measure the FFR just proximal to the side branch ostium, thus excluding the influence of lesions proximal to the side branch. Finally the pressure guidewire was completely pulled back into the guiding catheter, and we verified that no drift had occurred during the procedure (14). Side branch stenosis was considered functionally significant when FFR of the side branch was ≤0.80 after stent implantation in the main vessel (15).

Clinical follow up for adverse cardiac events, including death, myocardial infarction, or target vessel revascularization, was performed at 1 month after procedure, and every 3 months thereafter during the follow-up period.

Statistical analysis. Continuous variables are expressed as means and standard deviations or median and interquartile range (IQR) and are compared using the Student *t* test or Mann-Whitney test when appropriate. Categorical characteristics are expressed as absolute numbers and percentages, and compared using chi-square test or Fischer exact test when appropriate. Correlations between QCA parameters and FFR were assessed by Spearman correlation analysis. Binary logistic regression analysis was performed to find the predictors of functionally significant side branch stenosis after stent implantation in the main vessel. Number of stents used in the main vessel, maximal balloon pressure, true bifurcation, lesion length of the side branch, DS, and MLD of the side branch were entered into the multivariate model, and backward stepping was used to determine the independent predictors. Receiver-operating characteristic curve analysis was performed to assess the discriminatory power of the QCA parameters, with MedCalc (MedCalc Software, Mariakerke, Belgium) used to determine sensitivity, specificity, positive predictive value, and negative predictive value with 95% confidence intervals (CIs). The optimal cutoff values of QCA parameters to determine functionally significant side branch stenosis were those with the highest sum of sensitivity and specificity. Furthermore, kappa statistics were used to evaluate the agreement between functional significance and QCA parameters. All p values were 2-sided, and p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, Illinois).

Results

The demographic and clinical characteristics of the study population are summarized in Table 1. Most bifurcations (89.6%) were located between the left anterior descending artery and diagonal branch. The reference vessel diameter of the proximal main vessel, distal main vessel, and side branch were 3.4 ± 0.4 mm, 3.1 ± 0.4 mm, and 2.5 ± 0.4 mm, respectively. In a total of 230 side branches, the median value of FFR of the side branches and main vessel proximal to the side branch ostium was 0.91 (IQR: 0.85 to 0.95) and 0.94 (IQR: 0.91 to 0.97), respectively, after stent implantation in the main vessel, with 41 (17.8%) side branches having FFR ≤0.80. In addition, only 24 (10.4%) side branches had FFR ≤0.75. Functional, angiographic, and procedural characteristics are shown in Table 2.

Table 1. Baseline Characteristics of Study Population (N = 230)

Mean age, yrs	61.1 ± 9.2
Men	164 (71.3)
Smokers	40 (17.4)
Hypertension	85 (37.0)
Diabetes	56 (24.3)
Hypercholesterolemia	74 (32.2)
Previous percutaneous coronary intervention	14 (6.1)
Previous myocardial infarction	4 (1.7)
Clinical diagnosis	
Stable angina	174 (75.7)
Unstable angina	49 (21.3)
Acute myocardial infarction	7 (3.0)
Mean left ventricular ejection fraction, %	61.6 ± 5.4
Vascular extent of disease	
1-vessel	144 (62.6)
2-vessel	67 (29.1)
3-vessel	19 (8.3)
Location of side branch	
Diagonal branch	206 (89.6)
Left circumflex artery	11 (4.8)
Obtuse marginal branch	11 (4.8)
Posterior descending artery	1 (0.4)
Posterolateral branch	1 (0.4)

Values are mean ± SD or n (%).

Angiographic parameters and FFR. Among the angiographic parameters before stent implantation in the main vessel, lesion length MLD, reference vessel diameters, and DS of the side branch and true bifurcation were associated with the side branches with FFR ≤0.80 after stent implantation in the main vessel. When DS of the side branch before stent implantation was classified into 3 groups (<30%, 30% to 50%, >50%), the incidence of a side branch with FFR ≤0.80 was 13.1%, 20.8%, and 38.1%, respectively (p = 0.015) (Fig. 1). In addition, balloon pressure applied to the main vessel stent was significantly higher in the side branches with FFR ≤0.80. However, mean FFR measured in the main vessel proximal to the side branch and the angiographic characteristics of the main vessel, including the location of its narrowest site, did not differ significantly between side branches with FFR ≤0.80 and >0.80.

Multivariable analysis identified DS (odds ratio [OR]: 1.04, 95% CI: 1.02 to 1.06, p = 0.001) of the side branch before stent implantation in the main vessel as an independent predictor of the side branches with FFR ≤0.80 after stent implantation in the main vessel (Table 3).

Regarding the angiographic parameters after stent implantation in the main vessel, side branches with FFR ≤0.80 had a higher degree of DS, a smaller MLD, and a smaller reference diameter of the side branch than side branches with FFR >0.80. Figure 2 shows a significant

Table 2. Angiographic and Procedural Characteristics According to the Functional Significance of the SB After Stent Implantation in the MV

	FFR <0.80* (n = 41)	FFR ≥0.80 (n = 189)	p Value
Functional assessment after main vessel stenting			
FFR, side branch	0.70 ± 0.09	0.90 ± 0.05	—
FFR, main vessel	0.93 ± 0.06	0.94 ± 0.04	0.48
Procedural characteristics at main vessel stenting			
Stent number	1.5 ± 0.6	1.4 ± 0.6	0.08
Stent size, mm	3.3 ± 0.2	3.3 ± 0.3	0.36
Stent length, mm	37.0 ± 13.2	33.4 ± 13.4	0.12
Maximal balloon pressure, atm	15.0 ± 5.0	13.4 ± 4.4	0.05
Maximal balloon diameter, mm	3.6 ± 0.3	3.6 ± 0.4	0.44
Angiographic analysis			
True bifurcation lesion†	18 (45.0)	43 (22.8)	0.004
Lesion length			
Main vessel	30.3 ± 12.0	26.5 ± 12.2	0.08
Side branch	3.5 ± 5.0	1.6 ± 4.0	0.012
Type A lesion	19 (46.3)	71 (37.6)	0.30
Proximal main vessel			
Before			
MLD, mm	1.7 ± 0.6	1.6 ± 0.5	0.62
Reference diameter, mm	3.3 ± 0.4	3.4 ± 0.4	0.50
DS, %	49.3 ± 19.7	55.1 ± 15.1	0.41
After			
MLD, mm	3.0 ± 0.4	3.0 ± 0.4	0.67
Reference diameter, mm	3.3 ± 0.3	3.3 ± 0.4	0.94
DS, %	10.8 ± 9.4	9.5 ± 7.3	0.42
Distal main vessel			
Before			
MLD, mm	1.6 ± 0.5	1.4 ± 0.5	0.11
Reference diameter, mm	3.0 ± 0.4	3.1 ± 0.4	0.22
DS, %	46.9 ± 19.0	51.6 ± 16.8	0.12
After			
MLD, mm	2.6 ± 0.5	2.7 ± 0.4	0.14
Reference diameter, mm	2.9 ± 0.3	2.9 ± 0.4	0.62
DS, %	9.7 ± 7.0	8.9 ± 6.5	0.47
Side branch			
Before			
MLD, mm	1.5 ± 0.5	1.8 ± 0.5	<0.001
Reference diameter, mm	2.4 ± 0.4	2.5 ± 0.4	0.05
DS, %	34.8 ± 17.8	26.3 ± 15.4	0.002
After			
MLD, mm	1.4 ± 0.6	1.7 ± 0.6	0.001
Reference diameter, mm	2.3 ± 0.5	2.5 ± 0.4	0.024
DS, %	45.5 ± 20.3	36.5 ± 17.1	0.004
Angles			
Before			
Proximal	148.9 ± 27.4	153.9 ± 24.9	0.26
Distal	57.2 ± 29.0	53.0 ± 25.6	0.35
After			
Proximal	152.2 ± 20.8	150.5 ± 23.9	0.64
Distal	49.4 ± 21.7	51.0 ± 22.4	0.69

Values are mean ± SD or n (%). *FFR measured immediately after simple cross-over stenting in the main vessel. †Medina classification of 1,1,1 (n = 44); 1,0,1 (n = 6); 0,1,1 (n = 13) by visual estimate.

DS = diameter stenosis; FFR = fractional flow reserve; MLD = minimal lumen diameter; MV = main vessel; SB = side branch.

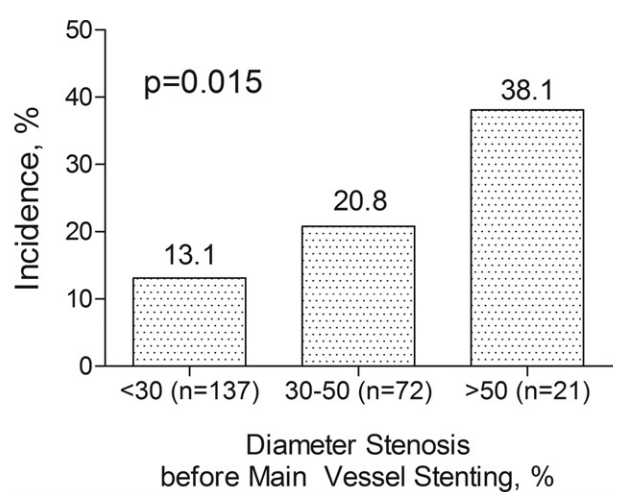

Figure 1. FFR and Pre-Interventional DS of Side Branches

Incidence of side branches with fractional flow reserve (FFR) ≤0.80 after stent implantation according to angiographic diameter stenosis (DS) of the side branch before stent implantation in the main vessel.

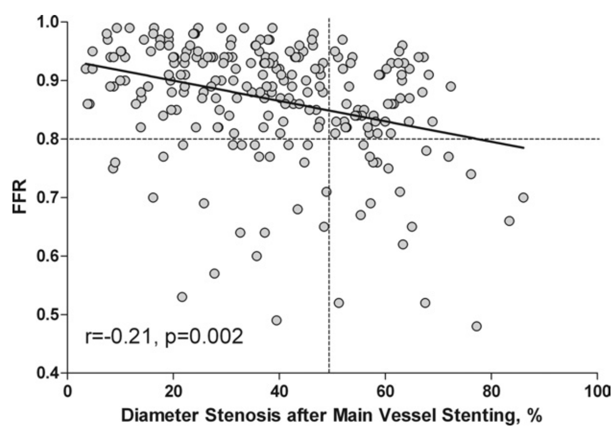

Figure 2. FFR and Post-Interventional DS of Side Branches

Scatter plot comparing FFR and angiographic DS of the side branch after stent implantation in the main vessel. The lines represent 50% DS and an FFR of ≤0.80. Abbreviations as in Figure 1.

inverse correlation between DS of the side branch after stent implantation in the main vessel and FFR in the side branches ($r = -0.21$, $p = 0.002$). However, there was wide variation in FFR values, regardless of the DS. Among 67 side branches with >50% stenosis, 19 (28.4%) had FFR ≤0.80 and among 163 side branches with ≤50% stenosis, 22 (13.5%) had FFR ≤0.80.

Using receiver-operating characteristic curve analysis, we found that the optimal cutoff value for DS of the side branch after stent implantation in the main vessel to discriminate between side branches with FFR ≤0.80 and those with FFR >0.80 was 54.9%, with a sensitivity of 41.5%, a specificity of 83.1%, a positive predictive value of 34.7%, a negative predictive value of 86.3%, and an accuracy of 75.7%. The area under the curve (AUC) for DS of the side branch after stent implantation at main vessel was 0.64 (95% CI: 0.58 to 0.71, $p < 0.001$), which indicated less accurate discriminatory power. MLD ($r = 0.29$, $p < 0.01$) and reference vessel diameter ($r = 0.14$, $p = 0.035$) of the side branch were also significantly correlated with FFR of the side branch, but they were also less accurate in discriminating between the functional significance and insignificance of side branches, with AUC of 0.67 and 0.63, respectively (16).

Treatment and clinical outcomes. After stent implantation in the main vessel, side branch treatment was performed in 76 lesions (kissing balloon inflation in 72 lesions and provisional T stenting in 4 lesions). Among the side branches with FFR ≤0.80, side branch treatment was performed in 19 (46.3%) lesions. Among the side branches with FFR >0.80, side branch treatment was performed in 56 (29.6%) lesions. During a median follow-up of 22.5 months (IQR: 15.2 to 28.9 months), only 1 death and 4 cases of target vessel revascularization occurred. In patients with initial FFR ≤0.80, 1 patient died due to stroke, and another patient had bypass surgery due to in-stent restenosis of the implanted stent in the main vessel. In patients with initial FFR >0.80, 2 patients had repeat percutaneous coronary intervention, and 1 patients had bypass surgery due to in-stent restenosis of the implanted stent in the main

Table 3. Pre-Interventional Angiographic Parameters Predictive of SBs With FFR ≤0.80

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Diameter stenosis of SB, %	1.04	1.02–1.06	0.001	1.04	1.02–1.06	0.001
Reference diameter of SB, mm	0.42	0.17–1.03	0.057	0.28	0.10–0.77	0.014
Maximal balloon pressure, atm	1.09	1.00–1.17	0.027	1.07	0.99–1.16	0.089
Minimal lumen diameter of SB, mm	0.23	0.11–0.51	<0.001			
Lesion length of SB, mm	1.08	1.01–1.16	0.02			
True bifurcation	2.93	1.45–5.92	0.003			

CI = confidence interval; other abbreviations as in Table 2.

vessel. There were no adverse clinical events related with side branches during follow-up.

Discussion

In this prospective registry of 230 bifurcation lesions that underwent FFR measurement of the side branches after stent implantation in main vessel, we found that: 1) in overall lesions, only 17.8% of side branches had functional significance; 2) pre-interventional angiographic DS of the side branch were independently associated with side branches having FFR ≤0.80 after stent implantation; and 3) although angiographic stenosis of side branches after stent implantation was significantly correlated with the FFR of those, its discriminatory power was limited in predicting the functional significance. Therefore, the determination of the functional significance of the side branch after stent implantation and treatment decisions for the jailed side branches should not be based on angiographic findings alone.

Angiographic assessment of coronary bifurcation lesions remains challenging. A previous pivotal study of FFR measurements of jailed side branches showed that angiographic stenosis was unreliable in the assessment of functional significance of side branches (9). In that study, only 27% of side branches with angiographic stenosis >75% had FFR ≤0.75, and none of the side branch lesions with angiographic stenosis <75% was associated with a functionally significant FFR. Therefore, angiographic stenosis was found to generally overestimate the functional severity of side branches.

We confirmed the previous findings in a large number of coronary bifurcation lesions, predominantly left anterior descending artery and diagonal branches, with only 28.4% of side branches with angiographically significant stenosis having FFR ≤0.80. However, our results were not entirely consistent with those of the previous study. We found that 13.5% of the side branches with angiographically insignificant lesions also had FFR ≤0.80. In addition, a widely distributed scatter plot was observed when the FFR value and DS of the side branch were compared. Therefore, the discriminative ability of angiographic DS assessed by an AUC in the current study was only 0.64, which was less accurate than in the previous report, with an AUC of 0.85 (9,16). This finding was also contradictory to the widespread concept that a moderate stenosis of the side branches is never functionally significant (17). However, angiographically insignificant, but functionally significant, stenoses have already been reported in intermediate left main coronary artery stenosis and diffuse coronary artery stenosis (18,19). In addition, a recently published bifurcation study showed that 29.4% of angiographically insignificant side branches were associated with an abnormal FFR, which supports our findings (12). This observation in the side branches may be explained by multiple plausible mechanisms, including the diffuse nature of coronary artery disease, the overlapping of vessel segments, and/or imaging foreshortening. However, the clinical impact of this remains to be evaluated in future investigations.

We used dedicated bifurcation QCA to assess the coronary bifurcation lesions. Conventional QCA analysis has overestimated DS of the side branch because of the discrepancy in vessel size proximal and distal to the carina (step-down phenomenon) when compared with dedicated bifurcation QCA (20). Therefore, DS of the current study tends to be lower than that of previous studies (9,10,12,21). In addition, a recent study demonstrated that dedicated bifurcation QCA was better correlated with the functional significance of the side branch (6). Nevertheless, no angiographic parameter was able to adequately predict the functional significance of side branches.

The DS of side branches and the location of the minimal lumen area, as assessed by intravascular ultrasound in the main vessel, were recently shown to be independent predictors of functionally significant side branch stenosis after stent implantation in the main vessel (12). Similarly, we also found that DS of side branches before stent implantation in the main vessel were predictive of functionally significant side branch stenosis. Therefore, it suggests that a relatively large side branch without significant angiographic ostial stenosis may be successfully treated by simple crossover stenting without serious concerns about the functional deterioration of the side branch.

The amount of myocardium supplied by the stenotic lesion may influence the functional significance (22). Therefore, a severe stenosis in a vessel supplying a small myocardial territory may not be functionally significant. In this context, the high incidence of angiographically significant, but functionally insignificant, stenosis in a side branch of a bifurcation, as high as 73.8% in the current study, can be understood. By contrast, a recently published substudy of FAME (Fractional flow reserve versus Angiography for Multi-vessel Evaluation) trial demonstrated that 36.3% of angiographically significant stenosis had FFR >0.80 in the epicardial coronary artery (23). However, such a discrepancy was also explained by multiple factors, including lesion length, reference vessel size, and eccentricity of the lesions, which are important contributing factors to flow resistance and abnormal FFR.

Practical application of FFR in the treatment of coronary bifurcation lesions. Most jailed side branches after main branch stent implantation did not have functionally significant stenoses and usually did not supply large enough regions of jeopardized myocardium to affect the patients' clinical outcomes, except in distal left main bifurcation. Therefore, complex stenting procedures or kissing balloon angioplasty after main vessel stent implantation did not always improve the clinical outcomes as long as the TIMI flow grade 3 was maintained in side branches (1–4).

Therefore, from a practical point of view, FFR measurements should be considered first to evaluate functional significance, when the operator intends to treat the jailed side branches supplying large regions of jeopardized myocardium or having a large vessel diameter. In this manner, unnecessary complex coronary procedures and their associated complications could be avoided.

Study limitations. First, intervention in a jailed side branch was at the discretion of the operator. The number of lesions with significant angiographic stenosis of the side branch ostium at baseline was relatively small, because most of these lesions had been treated by a systematic 2-stent strategy. Moreover, technical difficulties were encountered in rewiring after stent implantation in the main vessel, and there was a risk of side branch ostial dissection during FFR measurement, although the pressure guidewires we used to measure FFR had handling characteristics similar to those of conventional angioplasty guidewires. Although we enrolled consecutive patients and lesions undergoing FFR measurement, the true incidence of functionally significant side branch stenosis may have been over- or underestimated. In addition, although several mechanisms of jailed side branches have been described (12), our angiographic analysis did not provide information on this issue. Finally, although we used a dedicated bifurcation QCA system, this system itself has inherent limitations in assessing the coronary artery tree and is not entirely free from the limitations of conventional QCA.

Conclusions

Most side branches do not have functional significance after stent implantation in the main vessel. Although several angiographic parameters appeared to be associated with the functional significance of side branches, QCA estimation of side branch stenoses was not reliable in predicting functional status.

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